Table 6: **Gag**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Gag(77–85)	Gag(77–85)	SLYNTVATL		human(HLA-A201)	[Sandberg (2000)]
• This epitope served as a positive control in a study comparing peptide binding affinity to HLA-A201 to CTL responses upon vaccination with a nef DNA vaccine					
Gag(223–231)	( )	GPGHKARVL		(B7)	[Brander & Goulder(2001), Goulder(1999)]
Gag( )	Gag( )		Vaccine	Rhesus macaque( )	[Paliard (2000)]
Vaccine: *Vector/type:* virus-like particle *HIV component:* gag					
• CTLs primed by HIV-1 p55 gag virus-like particle (VLP) vaccination recognized epitopes in four different 20 amino acid peptides p17/4, p17/8, p24/13 and p14/9					
• Cytotoxic T-cell response lasted greater than 8.5 months					
Gag( )	Gag( )		HIV-1 infection	human( )	[Wasik (2000)]
• HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of β-chemokines and IL-2 relative to other HIV+ infants					
• No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors					
• CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs					
Gag( )	Gag( )		Vaccine	human( )	[Salmon-Ceron (1999)]
Vaccine: *Vector/type:* canarypox *Strain:* LAI, MN *HIV component:* gp41, Gag, Pro, V3					
• The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))					
• Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36					
• Immunization with vCP205 induced HIV-1-specific ABs to gp160, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160					
Gag( )	p24( )		Vaccine	human( )	[Klein (1997)]
Vaccine: *Vector/type:* virus-like particle *HIV component:* p24, p17					
• Immunization of HIV+ people with an HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load					
• Two of four subjects that received 500 or 1000 μg of p24-VLP had an increase in gag-specific CTL					

Gag( )	p24( )	Vaccine	murine, baboon( )	[O'Hagan (2000)]

Vaccine: *Vector/type:* DNA *Strain:* SF2 *HIV component:* gp120, p24 *Stimulatory Agents:* PLG-microparticle, MF59 adjuvant

- PLG (Polylactide co-glycolide polymer) microparticles administered in MF59 emulsion induced gp120 Ab responses and CTL immune responses against p24 gag

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Gag( )	Gag( )	HIV-1 infection	human( )	[Lubaki (1999)]

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20

Gag( )	Gag( )	HIV-1 infection	human( )	[Kalams (1999a)]

- The presence of HIV-1 p24-specific proliferative responses was positively correlated with Gag-specific memory CTL and negatively correlated with viral load in untreated subjects
- Gag proliferative responses were the most readily detected – Gag CTL responses were the only responses with a significant correlation with Gag stimulated help, although there was a positive trend with Nef, Env and RT

Gag( )	p55( )	HIV-1 infection	human( )	[Greenough (1999)]

- 7/128 HIV-1 infected hemophiliacs were identified as long-term non-progressors (LTNPs) and were monitored for viral and host immune parameters over 15 years – LTNPs maintained a low viral load, high frequencies of CTL precursors directed against Gag antigen and low levels of HIV-specific effector CTL activity – effector cell activity suggests low level ongoing viral replication

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Gag( )	Gag( )	HIV-1 infection	human( )	[Trickett (1998)]

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection
- Improvement in CD4+ and CD8+ T-cells was seen in 7/12, and an increase in the CTL response to Gag was seen in one patient

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Gag( )	Gag( )	HIV-1 infection	human( )	[Betts (1999)]

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection

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Gag( )	Gag( )	HIV-1 infection	human( )	[Legrand (1997)]

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef
- Early responses to Pol, Rev, Vif and Tat were rare

Gag( )	Gag( )	HIV-1 infection	human( )	[Betts (1997)]

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients

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Gag( ) Gag( ) HIV-1 infection human( ) [De Maria (1997)]

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T-cell function
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels

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Gag( ) Gag( ) Vaccine human( ) [Belshe (1998)]

Vaccine: *Vector/type:* canarypox prime with rgp120 boost *Strain:* MN, LAI, SF2 *HIV component:* gp120, gp41, Gag, Protease

- The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers

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Gag( ) Gag( ) HIV-1 infection human( ) [Buseyne (1998a)]

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load

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Gag( ) Gag( ) HIV-1 infection human( ) [Buseyne (1998b)]

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes

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Gag( ) Gag( ) HIV-1 exposed seronegative human( ) [Goh (1999)]

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins

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Gag( ) Gag( ) Vaccine human( ) [Evans (1999)]

Vaccine: *Vector/type:* canarypox *HIV component:* gp120, gp41, Gag, Pro, Nef, RT

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination

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Gag( ) p17( ) HIV-1 infection human( ) [Kuiken (1999)]

- A correlation between conserved regions of p17 or Nef and CTL epitope density was noted – the authors suggest that this may be due to a biological reason such as epitope processing, or may possibly be an artifact of experimental strategy for epitope definition such that conserved epitopes would tend to be identified because they would be more likely to be cross-reactive with the test reagents
- In contrast to p17 and Nef, p24 is a more conserved protein and known epitopes are evenly distributed across p24

Gag( ) Gag( ) Vaccine Macaca nemestrina( ) [Kent (1998)]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *Strain:* LAI *HIV component:* Env, Gag

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a decrease in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced

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Gag( ) Gag/Pol( ) Vaccine human( ) [Salmon-Ceron (1999)]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers

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Gag( ) Gag/Pol( ) Vaccine chimpanzee( ) [Kim (1998)]

Vaccine: *Vector/type:* DNA *HIV component:* Env, Gag, Pol *Stimulatory Agents:* CD86, CD80

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Gag( ) Gag( ) HIV-1 infection human( ) [Aladdin (1999)]

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death

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Gag( ) Gag( ) Vaccine Rhesus macaque( ) [Akahata (2000)]

Vaccine: *Vector/type:* DNA *Strain:* ZF1 *HIV component:* complete genome

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging
- Env and Gag specific CTL, but no antibody responses, were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response
- PBMC from all vaccinated monkeys produced IFN-γ, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit

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Gag( ) Gag( ) HIV-1 infection human( ) [Salerno-Goncalves (2000)]

- A general test of CD8 anti-viral activity was developed based on proviral load of coculture of autologous CD8+ cells with CD4+ cells after homogeneous superinfection with NSI virus
- Significantly decreased CD4+ T-cell proviral loads were found in 12 HIV+ slow progressors relative to 10 rapid progressors

- Significant CD8+ mediated cytotoxicity directed against autologous cells infected with vaccinia carrying the HIV-1 gag gene was observed in slow progressors in contrast to rapid progressors, but no correlation was found between plasma viral load in 22/22 asymptomatic HIV infected individuals

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Gag( ) Gag( ) none HIV-1 infection human( ) [Young (2001)]

- Addition of recombinant human IL-12 (rhIL-12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had > 500 CD4 cells/μl
- 2/10 individuals with <200 CD4 cells/μl, and 3/10 individuals with 200-500 CD4 cells/μl, had an increase of >5% upon treatment of the culture with rhIL-12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL-12

Gag( ) ( ) none HIV-1 infection murine( ) [de Quiros (2000)]

- CB-17 SCID-Hu mice engrafted with peripheral blood mononuclear cells of four long-term nonprogressors (viral load < 50 copies/ml) displayed resistance to challenge with HIV-1 SF162, mediated by CD8+ T-cells and associated with proliferation in response to p24 – these patients did not have a higher level of HIV-1 specific immunity *in vitro*, so the mechanism is unknown

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Gag( ) Gag( ) HIV-1 infection human( ) [Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype

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Gag( ) Gag( ) none HIV-1 infection human( ) [White (2001)]

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women

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Gag( ) Gag( ) none HIV-1 infection human( ) [Chun (2001)]

- Suppression of viral replication in the resting CD4+ T-cell reservoir by autologous CD8+ T-cells via CD4+/CD8+ cell contacts was observed in long-term nonprogressors and patients undergoing antiretroviral treatment, but this activity appears to be independent of Gag-specific CTL activity

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Gag( ) Gag( ) HIV-1 infection human( ) [Jin (2000a)]

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets
- LTNPs have high memory CTL numbers and low viral load

Gag( ) Gag( ) HIV-1 exposed seronegative human( ) [Rowland-Jones (2001)]

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays

- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T-cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T-cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people

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Gag( ) | Gag( ) | HIV-1 infection | human(A*0201, Cw*08) | [Shacklett (2000)]

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples

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Gag( ) | p24( ) | Vaccine | murine(H-2^d) | [Qiu (2000)]

Vaccine: *Vector/type:* DNA *HIV component:* gag

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors
- IFN-γ levels were increased compared to an undetectable IL-4 response
- CTL levels were also increased in secreted Gag expression vaccination studies

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Gag( ) | Gag( ) | Vaccine | murine(H-2^d) | [Huang (2001)]

Vaccine: *Vector/type:* DNA *Strain:* gag HxB2, pol NL43 *HIV component:* Gag, Pol

- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti-Pol CTL

Gag( ) | p24( ) | Vaccine | murine(H-2^b, H-2^d, H-2^k) | [Iroegbu (2000)]

Vaccine: *Vector/type:* DNA *HIV component:* p17/p24

- The p24 sequence is more conserved than is p17 within patient, and nonsynonymous substitutions are spread evenly throughout its coding regions, not concentrated in CTL epitopes
- Minor changes in p24 did not alter the immunogenicity in H-$2^{b,d,k}$ mice, while changes in p17 (92% similarity) did alter immunogenicity

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Gag( )	Gag( )		Vaccine	murine(H-2^{bxd})	[Otten (2000)]

Vaccine: *Vector/type:* DNA, vaccinia *Strain:* SF2 *HIV component:* codon-optimized gag and pol

- CB6F1 were primed with gag DNA by i.m. injection and challenged with vaccinia expressing Gag/Pol (rVVgag-pol)
- Gag-specific CTL responses were detected by IFNγ secretion in the spleen, independent of the route (intraperitoneal, intranasal or intrarectal) of rVV gag-pol challenge
- The gag DNA vaccine induced CTL responses in 4/4 monkeys 2 weeks post immunization, but antibody responses were detected in only 1/4 monkeys after 3 immunizations
- CTL cross-reactivity against Gag sequences 1–80, 254–323, and 421–496 was observed, suggesting multiple CTL epitope recognition

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Gag( )	Gag( )		Vaccine	Rhesus macaque, murine(H-2^{d})	[zur Megede (2000)]

Vaccine: *Vector/type:* vaccinia *Strain:* SF2 *HIV component:* Gag, Protease, codon-optimized

- Sequence-modified Rev-independent gag and gag-protease gene constructs lead to increased expression levels and elevated CTL and antibody immunogenicity in BALB/c and CB6F1 mice
- A CTL response in mice could be detected after a single immunization with codon-optimized gag, using 2 ng of plasmid; wild type gag required 200 ng to detect a response
- Recognition of 3 different Gag peptide pools was observed, indicating a polyclonal CTL response
- Significant gag-specific CTL responses were detected in 4/4 rhesus monkeys, in contrast to 1/4 using wildtype gag

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Gag( )	p24( )		Vaccine	murine(H-2^{d})	[Halim (2000)]

Vaccine: *Vector/type:* coxsackievirus *HIV component:* partial p24, polyepitope

- An avirulent recombinant coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T help responses can be elicited from peptides embedded in a surface loop of the VP1 capsid
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice

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Gag( )	Gag( )	none	Vaccine	murine(H-2^{d}, H-2^{b})	[Mata (2001)]

Vaccine: *Vector/type:* Listeria monocytogenes *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag
- Gag-specific CTL may enhance viral clearance via IFN-γ secretion, but are not essential for immunity

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Gag( )	Gag( )	none	Vaccine	murine(H-2^d, H-2^b)	[Mata & Paterson(2000)]

Vaccine: *Vector/type:* Listeria monocytogenes *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways
- This article is a review of L. monocytogenes biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cells mediated Gag specific immunological protection in mice and the Gag CTL response